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JOHN P. IWANICKI			RICIGLIANO,J		
	ITCOFF, LTD			ART UNIT	PAPER NUMBER
28 STATE S' BOSTON MA	T., 28TH FLM 02109	₹.	٠	1627	31
				DATE MAILED:	07/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No. 08/574,461 Applicant(s)

Examiner

Joseph W. Riciglian

Group Art Unit

Barone et al.

1627

X Responsive to communication(s) filed on <u>May 26, 2000</u>					
☐ This action is FINAL .					
☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle35 C.D. 11; 453 O.G. 213.					
A shortened statutory period for response to this action is set to expire longer, from the mailing date of this communication. Failure to respond with application to become abandoned. (35 U.S.C. § 133). Extensions of time m 37 CFR 1.136(a).	nin the period for response will cause the				
Disposition of Claim					
	is/are pending in the applicat				
Of the above, claim(s)	is/are withdrawn from consideration				
Claim(s)	is/are allowed.				
	is/are rejected.				
Claim(s)	is/are objected to.				
☐ Claims	are subject to restriction or election requirement.				
Application Papers See the attached Notice of Draftsperson's Patent Drawing Review, PT The drawing(s) filed on	y the Examiner. S ☐ approved ☐disapproved. S.C. § 119(a)-(d). documents have been				
☐ received in Application No. (Series Code/Serial Number) ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).					
*Certified copies not received:					
Acknowledgement is made of a claim for domestic priority under 35 L	J.S.C. § 119(e).				
Attachm nt(s) Notice of References Cited, PTO-892 Information Disclosure Statement(s), PTO-1449, Paper No(s). Interview Summary, PTO-413 Notice of Draftsperson's Patent Drawing Review, PTO-948 Notice of Informal Patent Application, PTO-152					
SEE OFFICE ACTION ON THE FOLLO	DWING PAGES				

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Continued Prosecution Application

1. The request filed on 5/26/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/574461 is acceptable and a CPA has been established. An action on the CPA follows.

2. This action is responsive to the amendment and response of 5/26/00. Claims 1-5, 10, 15 and 39 have been amended. Claims 1-8, 10-15, 37-39 are pending and being examined on their merits.

Claim Rejections - 35 USC § 112

3. Claims 1-8, 10-15, 37-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' claims are directed to a method of monitoring polymer array synthesis which encompass a genus of polymers that is indefinitely large and includes libraries of: carbohydrates, polyolefins, polysulofones, polyureas, polycarbonates etc. However, specification discloses only peptide and nucleotide libraries which is neither representative of the claimed genus nor representative of a substantial portion of the claimed genus. As the claimed libraries are recited only as diverse polymers one of ordinary skill in the art would not recognize that applicants were in possession of the necessary and common attributes or features of the genus members their methods of preparation and labeling in a planar array especially when the number of monomers is to be exactly limited. Moreover, the claimed genus encompasses diverse polymer libraries which

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are yet to be prepared or envisioned, which further evidences that the disclosed structural features of libraries (they are polymers made of monomers) do not constitute support for the claimed genus or a substantial portion of the claimed genus.

4. Claims 1-8, 10-15, 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleotides, peptides and peptide nucleic acids does not reasonably provide enablement and array of diverse polymers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-8, 10-15, 37-39 are directed toward a method of monitoring polymer array synthesis. The disclosure teaches the synthesis and addition of a label to DNA and peptide polymer arrays, subsequent cleavage of the array and analysis of the resulting mixture of polymers wherein the individual members of the array are detected by a property of the label added. However, the preparation of arrays of diverse arrays of polymers, especially those limited of length (specific number of units) and incorporation of labels into any polymer does not appear to be within the scope of reasonable experimentation. The factors to be considered in a determination of undue experimentation are disclosed in *In re Wands*, (U.S.P.Q. 2d 1400 (CAFC 1988)). The factors to be considered include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability of the art and the breadth of the claims.

A number of factors would prevent one of skill in the art from practicing the invention

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without undue experimentation, these are summarized as follows:

- 1) The specification fails to give adequate direction and guidance in the preparation of arrays of polymers commensurate in scope with "diverse polymers" as set forth in the claims. Moreover, as one must be able to control the length of the polymers in the claims to a specified number of monomers the chemistry used for preparation of many polymers (bulk homogeneous and heterogeneous catalysis) cannot be applied. Moreover, there is no teaching commensurate with the required incorporation of labels into "diverse polymers," only the incorporation of labels into peptides, and nucleotides.
- 2) Applicants have failed to provide working examples that are commensurate in scope with the unlimited polymers claimed.
- 3) The breadth of the claims encompasses a literally any polymer such as the polyolefin, methacrylate, polycarbonates, carbohydrates, polysulfones etc.
- 4) The state of the prior art is such that methods of preparing polymers limited in the exact number of monomeric units is not widely practiced except in the nucleotide and peptide areas.

 Thus, one has to develop synthetic routes capable of limiting the exact number of monomeric units incorporated into any polymer (generally by step wise addition of monomers) and means of labeling the corresponding resulting polymers.
- 5) The art is inherently unpredictable because predicting a priori how to prepare any single polymer cannot be done with certainty. The situation is compounded by the necessity that the chemistry must be flexible enough to accommodate differing subunits and still result in the production of the expected member in each position of the array.

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Therefore, while it is true that the level of skill in the art is high, it would require undue experimentation to make and use the invention commensurate in scope with that claimed in the absence of explicit guidance as to a means of preparing and labeling any polymer as set forth above.

Claim Rejections - 35 USC § 102/103

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.
- 6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
 - (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-8, 10-15 and 37-39 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lam *et al* [5,640,489; 102(e) date of at

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With respect to independent claims 1 and 10. Lam *et al* teach the synthesis of random biooligomers (which reads on diverse polymers, see abstract) which may be peptides or
oligonucleotides or a peptide oligonucleotide chimera (col. 5, lines 8-17). Lam *et al* teach the
synthesis of the oligomers using the split and combine method whereby individual beads are used
to synthesize one polymer per bead (figure 1). Lam *et al* teach synthesizing arrays of polymers
using different protocols in order to compare the results of the synthetic process on the array
produced. Lam *et al* also teach separately cleaving the collections of polymers from the support
beads to form separate mixtures and measuring the components present via a property (UV
absorbance in this instance) which reads on measuring a "property" (the composition) of the
mixture of unbound polymers as an indicator of the efficiency of the synthesizing step (see figure
3 and col. 34, line 60 - col. 35, line 55). In that the array of polymers produced in one method is
compared to the array produced in the second method one array reads on a reference array. Lam *et al* also teach several alternative embodiments for the preparation of polymeric arrays

With respect to the dependent claims:

In that the 215 nm absorbance by the exemplified peptides in Figure 3 is due to the amide bonds of the backbone the polymers comprise a label as required by claim 39. [That the absorbance at 215 nm is due to the amide backbone is well known in the art. However, the examiner has attached pages 161-162 of *Spectrophotometric identification of Organic Compounds (2nd ed, 1967)* for applicants convenience which clearly evidences this assertion.]. Additionally, it is noted that the indole ring of tryptophan or the phenyl ring of phenylalanine can serve as a detectable

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label at 280 nm (see Lam et al col. 33, lines 55-57). Therefore, Lam et al additionally reads on instant claim 39. In that each of the peptides in the exemplified arrays contain a tryptophan they comprise a single isomer as required by claim 2. Lam et al also teach that it is known to prepare libraries where the length of the polymer (number of monomeric units) is different as required by claims 3-5, col. 38 lines 60-65.

In that Lam *et al* teach the use of reverse phase HPLC to monitor the composition of the oligomer mixtures cleaved from the array, Lam *et al* render obvious the use of other well-known HPLC methods, which in view of applicants' disclosure of prior art teachings are notoriously well known and established in the art (see pages 38 and 39 of the specification). In addition, the analyses of mixtures of materials by gel electrophoresis as required in claim 5, especially the analysis of peptides and nucleotides is notoriously well known in the art as clearly evidenced by applicants' reliance on standard texts, laboratory manuals and manufacturers' literature, see page 38 and 39 of the specification.

Lam et al specifically recites the oligomers of the array can be oligonucleotides as required in claims 8 and 11 (col. 5, lines 8-17). Lam et al teach that the use of cleavable linkers, as required by claim 13, are well known in the art (col. 16, lines 10-40). In that the peptides exemplified by Lam et al were detected by their absorbance at 215 nm (see figure 3 left axis) they clearly are comprised of a detectable label as defined by applicant on page 12 of the specification and required in claim 14. In that the backbone amide chromophore comprises a single isomer and alternatively the indole of tryptophan comprises a single isomer (which is also fluorescent)

Lam et al reads on claims 14, 15 and 37-38. Lam et al also teach different embodiments polymer

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array libraries are known in the art including planar arrays (i.e., spatially addressable arrays of Fodor et al), see for example col. 3, lines 47-52. Therefore, while the preparation of libraries on planar arrays and their analysis is not the preferred embodiment set forth in Lam et al it is an immediately envisioned embodiment and hence the reference anticipates the invention of the instant claims.

In the alternative, one could argue that Lam et al did not actually prepare and analyze the arrays of polymeric molecules on planar supports and hence conduct the methods set forth in the instant claims. However, it would have been prima facia obvious to one of ordinary skill in the art at the time that the invention was made to analyze arrays made on planar supports by cleaving array members off and analyzing for their presence as taught by Lam et al because Lam et al teach the analysis of arrays of molecules which have been prepared and that planar arrays are known in the art. One of ordinary skill in the art would have been motivated to do so in order to be able to analyze the arrays made in different protocols which Lam et al teach is desirable. One of ordinary skill in the art would have reasonably expected to be successful as Lam et al had taught the analysis of molecules released from an array.

8. Claims 1-8, 10-15 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al [5,640,489; 102(e) date of at least 7/2/91] in view of Fodor et al [Science 251: 767 (1991)] and applicants' disclosure of the prior art teachings.

With respect to independent claims 1 and 10: Lam et al teach the synthesis of random biooligomers (which reads on diverse polymers, see abstract) which may be peptides or oligonucleotides or a peptide oligonucleotide chimera (col. 5, lines 8-17). Lam et al teach the

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synthesis of the oligomers using the split and combine method whereby individual beads are used to synthesize one polymer per bead (figure 1). Lam *et al* teach synthesizing arrays of polymers using different protocols in order to compare the results of the synthetic process on the array produced. Lam *et al* also teach separately cleaving the collections of polymers from the support beads to form separate mixtures and measuring the components present via a property (UV absorbance in this instance) which reads on measuring a "property" (the composition) of the mixture of unbound polymers as an indicator of the efficiency of the synthesizing step (see figure 3 and col. 34, line 60 - col. 35, line 55). In that the array of polymers produced in one method is compared to the array produced in the second method one array reads on a reference array. Lam *et al* also teach several alternative embodiments for the preparation of polymeric arrays

With respect to the dependent claims:

In that the 215 nm absorbance by the exemplified peptides in Figure 3 is due to the amide bonds of the backbone the polymers comprise a label as required by claim 39. [That the absorbance at 215 nm is due to the amide backbone is well known in the art. However, the examiner has attached pages 161-162 of *Spectrophotometric identification of Organic Compounds (2nd ed, 1967)* for applicants convenience which clearly evidences this assertion.]. Additionally, it is noted that the indole ring of tryptophan can serve as a detectable label at 280 nm (see Lam *et al* col. 33, lines 55-57). Therefore, Lam *et al* additionally reads on instant claim 39. In that each of the peptides in the exemplified arrays contain a tryptophan they comprise a single isomer as required by claim 2. Lam *et al* also teach that it is known to prepare libraries where the length of the polymer (number of monomeric units) is different as required by claims 3-5, col. 38 lines 60-65.

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In that Lam *et al* teach the use of reverse phase HPLC to monitor the composition of the oligomer mixtures cleaved from the array, Lam *et al* render obvious the use of other well-known HPLC methods, which in view of applicants' disclosure of prior art teachings are notoriously well known and established in the art (see pages 38 and 39 of the specification). In addition, the analyses of mixtures of materials by gel electrophoresis as required in claim 5, especially the analysis of peptides and nucleotides is notoriously well known in the art as clearly evidenced by applicants' reliance on standard texts, laboratory manuals and manufacturers' literature, see page 38 and 39 of the specification.

Lam et al specifically recites the oligomers of the array can be oligonucleotides as required in claims 8 and 11 (col. 5, lines 8-17). Lam et al teach that the use of cleavable linkers, as required by claim 13, are well known in the art (col. 16, lines 10-40). In that the peptides exemplified by Lam et al were detected by their absorbance at 215 nm (see figure 3 left axis) they clearly are comprised of a detectable label as defined by applicant on page 12 of the specification and required in claim 14. In that the backbone amide chromophore comprises a single isomer and alternatively the indole of tryptophan comprises a single isomer (which is also fluorescent) Lam et al reads on claims 14, 15 and 37-38. Lam et al also teach different embodiments polymer array libraries are known in the art including planar arrays (i.e., spatially addressable arrays of Fodor et al), see for example col. 3, lines 47-52. Lam et al did not actually prepare and analyze the arrays of polymeric molecules on planar supports and hence conduct the methods set forth in the instant claims.

Fodor et al teach the synthesis of polymer arrays on planar substrates where each member

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of the polymer array occupies a different region of the substrate.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to monitor the synthesis of polymer arrays synthesized on a planer support as taught by Fodor using a method of analysis as taught by Lam et al, because Lam et al teach the desirability of monitoring polymer array synthesis in order to compare the methods utilized in the synthetic process (see example 7 "Comparison of the claimed method with the conventional method of peptide synthesis" starting in column 7 at line 60) which is applicable to arrays synthesized on any support(s). One of ordinary skill in the art would have been motivated to do so in order to compare array synthesis protocols and optimize array synthesis (which is desirable whether the array has been prepared on a planar support or spherical supports, segmental supports, fiber supports... as are each are known in the art) as taught by Lam et al (loc cit.). One ordinary skill in the art would reasonably have expected to be successful because the basic method of preparing an array of oligomers on supports, cleaving them to form a mixture of oligomers and analyzing them had already been conducted by Lam et al. One of ordinary skill in the art would also have reasonably expected the use of gel electrophoresis, and HPLC chromatography to be successful because these are notoriously well known methods of analysis which have been applied to oligomeric compounds such as peptides and nucleotides. In addition it would have been prima facia obvious to one of ordinary skill in the art to vary synthesis protocols using only one variation as required by claim 12 because this would permit the analysis of changing one parameter. One of ordinary skill in the art would have been motivated to vary only one parameter at a time in order to be able to determine the effect of that altering that parameter on the out come

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of the experiment which is not possible when altering multiple parameters simultaneously. One of ordinary skill in the art would have reasonably expected to be successful altering one variable and looking at the outcome as Lam et al had not only developed and taught the methods of comparing peptides released from a peptide library but had also successfully compared the released peptides.

9. Applicants' arguments filed 9/20/99 have been fully considered but they are not persuasive.

Applicants' assert that Lam et al provides no motivation that it may be modified in the manner suggested by the examiner and that lame is directed to the use of resin beads and not to planer surfaces. Applicants assert that Lam provides no guidance for creating diverse polymers on a planer surface. Applicants conclude from the aforementioned arguments that Lam provides no reasonable expectation of success in using planer supports.

Applicants' arguments have been considered but are not found persuasive. The assertion that Lam et al provide no motivation to be modified to use planer supports is not found persuasive because Lam et al clearly set forth the desirability of comparing synthesis protocols (i.e., determining the synthesis efficiency etc...) Applicants' next assertion that Lam is limited to resin beads and not to planer surfaces is also not persuasive as the chemistry set forth Lam et al and required by the rejection of record would not be affected by required would not be affected by the shape of the synthesis support. Moreover, the argument fails to consider the teaching of Fodor et al. Applicants last assertion Lam et al provide no guidance for creating diverse polymers on a planer surface is not persuasive as it does not take into account the teachings of Fodor et al which were cited for this purpose. Therefore, the rejection is maintained for the

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reasons above and for the reasons of record in paper number 23.

Applicants' arguments filed 5/26/00 have been fully considered but they are not persuasive.

Applicants argue that Lam et al fail to teach 1) formation of polymer arrays on a planar surface, 2) cleaving the polymers from the surface 3) and measuring the polymers as a measure of the efficiency step. This argument is not found persuasive as Fodor et al was cited for the teaching of polymer array preparation on a planar surface (applicants' point 1) and Lam et al teach both the cleavage of polymer arrays from support surfaces and their analysis (applicants' points 2 and 3). Applicants' assertions are based upon a piecemeal analysis of the references rather than an analysis of the references as combined.

Applicants also argue that the Lam et al reference provides no motivation to combine the references and that it teaches away because it teaches using solid phase supports which are attached to a single biooligomer species (e.g., beads) and that Lam et al teach the limitations of Fodor et al. These arguments are not found persuasive because as set forth in MPEP 2142:

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." As Lam et at teach the desirability of analyzing synthesized arrays of molecules Lam satisfies the requirement for motivation as being one of the references themselves and by demonstrating the knowledge generally available to one of ordinary skill in the art. Moreover, the assertion that Lam et al teaches away by teaching the use of bead supports and because the reference discusses the limitations of Fodor et al is not persuasive. The argument is not persuasive because the

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reference does not state that the analysis cannot be done on planar supports or results in an in operative embodiment. The reference merely sets forth that in the opinion of Lam et al there are limitations of planar array, hence this would not be the preferred embodiment. It should also be noted that limitations referred to are not in the analysis of the arrays which are the subject of the instant claims but in the size of the arrays and techniques for generating the arrays.

10. Claims 1-8, 10-15 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al [5,640,489; 102(e) date of at least 7/2/91] in view of Holmes [US 5,679,773] and applicants' disclosure of the prior art teachings.

See the teachings of Lam et al and applicants' disclosure of the prior art teaching as applied to claims 1-8, 10-15 and 37-39 under 35 USC 103(a) as being unpatentable over Lam et al in view of Fodor and applicants disclosure of the teachings of the prior art, supra.

Holmes et al teach the synthesis of polymer arrays on planar substrates where each member of the polymer array occupies a different region of the substrate and the desirability of determining the fidelity of synthesis of such arrays (column 19, lines 33-58).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to monitor the synthesis of polymer arrays synthesized on a planer support as taught by Holmes using a method of analysis as taught by Lam et al, because Lam et al teach the desirability of monitoring polymer array synthesis in order to compare the methods utilized in the synthetic process (see example 7 "Comparison of the claimed method with the conventional method of peptide synthesis" starting in column 7 at line 60) which analyze mixtures of polymers cleaved from the support and Holmes teaches the desirability of determining the fidelity of array

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synthesis on planar supports by cleaving the polymers from the support. One of ordinary skill in the art would have been motivated to do so in order to compare array synthesis protocols and the resulting fidelity of array synthesis as suggested by Lam *et al* and Holmes. One ordinary skill in the art would reasonably have expected to be successful because the basic method of preparing an array of oligomers on supports, cleaving them to form a mixture of oligomers and analyzing them had already been conducted by Lam *et al*. One of ordinary skill in the art would also have reasonably expected the use of gel electrophoresis, and HPLC chromatography to be successful because these are notoriously well known methods of analysis which have been applied to oligomeric compounds such as peptides and nucleotides.

11. Applicants' arguments filed 9/20/99 have been fully considered but they are not persuasive.

Applicants assert that Lam et al provides no motivation that it may be modified in the manner suggested by the examiner and that lame is directed to the use of resin beads and not to planer surfaces. Applicants assert that Lam provides no guidance for creating diverse polymers on a planer surface. Applicants conclude from the aforementioned arguments that Lam provides no reasonable expectation of success in using planer supports.

Applicants' arguments have been considered but are not found persuasive. The assertion that Lam et al provide no motivation to be modified to use planer supports is not found persuasive because Lam et al clearly set forth the desirability of comparing synthesis protocols (i.e., determining the synthesis efficiency etc...) and Holmes sets forth the desirability of monitoring synthesis fidelity. Applicants' next assertion that Lam et al are limited to resin beads

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and not to planer surfaces is also not persuasive as the chemistry set forth Lam et al, required by the rejection of record, would not be affected by the shape of the synthesis support. Moreover, the argument fails to consider the teachings of Holmes. Applicants last assertion Lam et al provide no guidance for creating diverse polymers on a planer surface is not persuasive as it does not take into account the teachings of Holmes which were cited for this purpose. Therefore, the rejection is maintained for the reasons above and for the reasons of record in paper number 12. Applicant's arguments filed 5/26/00 have been fully considered but they are not

- 12. Applicant's arguments filed 5/26/00 have been fully considered but they are not persuasive. Applicants argue that Holmes et al fail to cure the deficiencies of Lam et al for the same reasons Fodor et al fail to cure the deficiencies of Lam et al. These arguments are not found persuasive for the reasons set forth above. The examiner also emphasizes that in addition to the motivation set forth by Lam et al for combining the references Holmes et al also discuss cleavage of the array members from the support and comparison with standards to provide a confirmation of synthesis fidelity.
- 13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor,

Jyothsna Venkat, can be reached at (703) 308-2439.

Joseph W. Ricigliano Ph. D.

DR. JYOTHSNA VENKAT PH.D SUPERVISORY PATENT EXAMINER TECHNOLOGY CENTER 1600